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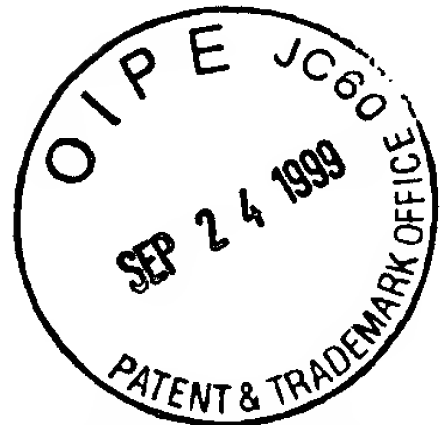
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September 24, 1999

Assistant Commissioner for Patents  
Washington, D.C. 20231

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SEP 27 1999  
TECH CENTER 1600/2900  
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(202) 789-5507

Re: U.S. Utility Patent Application  
Appl. No. 09/028,514; Filed: February 23, 1998  
For: **Serum-Free Mammalian Cell Culture Supplement, and Uses Thereof**  
Inventors: Gorfien *et al.*  
Our Ref: 0942.4110002/RWE/GER

Sir:

Transmitted herewith for appropriate action are the following documents:

1. First Supplemental Information Disclosure Statement;
2. A listing of the forty-seven (47) cited documents on Form PTO-1449 (12 sheets);
3. A copy of each document listed on Form PTO-1449; and
4. One (1) return postcard.

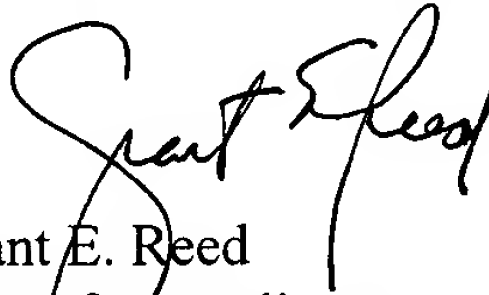
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Assistant Commissioner for Patents  
September 24, 1999  
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Enclosures

Applicants: Gorfien *et al.*

Due Date: None

Art Unit: 1651

Examiner: D. Ware

Application No.: 09/028,514

Docket: 0942.4110002

Filed: February 23, 1998

Atty: RWE/GER

For: Serum-Free Mammalian Cell Culture Medium, and Uses Thereof

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. PTO Transmittal Letter (*in duplicate*);
2. First Supplemental Information Disclosure Statement;
3. A listing of the forty-seven (47) cited documents on Form PTO-1449 (12 sheets);
4. A copy of each document listed on Form PTO-1449; and
5. One (1) return postcard.



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#7 w/attach's

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

GORFIEN *et al.*

Appl. No. 09/028,514

Filed: February 23, 1998

For: **Serum-Free Mammalian Cell  
Culture Supplement, and Uses  
Thereof**

Art Unit: 1651

Examiner: D. Ware

Atty. Docket: 0942.4110002/RWE/GER

**First Supplemental Information Disclosure Statement**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each document is submitted herewith. The numbering on this First Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Information Disclosure Statement filed on August 11, 1998 in connection with the above-captioned application.

Document AN2 is in a foreign language. Document AN2 is believed to relate to the use of hydrolysates of wheat gluten, with or without the addition of yeast extract, to promote *in vitro* growth of animal cells. An English language abstract of document AN2 is also provided (Document AR11).

The Examiner's attention is directed to co-pending U.S. Patent Application No. 09/302,953, filed April 30, 1999, which may be directed to related technical subject matter. The identification of this U.S. Patent Application is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited application.

Following is a statement of facts for consideration by the Examiner.

***I. Priority Applications***

The present application was filed February 23, 1998. As indicated in the Declaration for Patent Application filed July 6, 1998, the present application claims priority benefit of the following applications:

U.S. provisional application no. 60/022,881, filed August 30, 1996;

U.S. provisional application no. 60/056,829, filed August 22, 1997;

U.S. non-provisional application no. 08/920,875, filed August 29, 1997; and

International application no. PCT/US97/15926, filed September 2, 1997.

The Declaration for Patent Application contains a typographical error: international application no. PCT/US97/15926 should read international application no. PCT/US97/15296.

***II. The "Suspension Culture Medium" and the "Replacement Medium"***

***A. Applications***

Two broad classes of media are disclosed in the present application: a "suspension culture medium," and a "replacement medium."

The suspension culture medium is disclosed and claimed in U.S. priority application no. 60/056,829, and in international application no. PCT/US97/15296.

The replacement medium is disclosed and claimed in U.S. priority application nos. 60/022,881 and 08/920,875, and in international application no. PCT/US97/15296.

**B. *Nomenclature of Replacement Media***

**1. *CHO-S-SFM***

The CHO-S-SFM medium is a serum-free medium that can be used to culture cells in suspension. The CHO-S-SFM medium is not chemically defined, contains protein, and is not free of animal-derived ingredients. The CHO-S-SFM medium contains a zinc salt, insulin and transferrin. The CHO-S-SFM medium does not contain an iron chelate.

**2. *CHO-S-SFM II***

The CHO-S-SFM II medium is a serum-free medium that can be used to culture cells in suspension. The CHO-S-SFM II medium is not chemically defined, contains protein, and is not free of animal-derived ingredients. The CHO-S-SFM II medium contains a zinc salt, insulin and transferrin. The CHO-S-SFM II medium does not contain an iron chelate.

**3. *CHO-A-SFM***

The CHO-A-SFM medium is a serum-free medium and is a variant of the CHO-S-SFM II medium that encourages anchorage-dependent growth. The CHO-A-SFM medium is not chemically defined, contains protein, and is not free of animal-derived ingredients. The CHO-A-SFM medium contains a zinc salt, insulin and transferrin. The CHO-A-SFM medium does not contain an iron chelate.

**4. *CHO III Prototype***

The CHO III Prototype medium is a serum-free medium that can be used to culture cells in suspension. The CHO III Prototype medium is not free of animal-derived ingredients. The CHO III Prototype medium is believed to be essentially protein-free, but it is not chemically

defined because it contains protein hydrolysate and lower molecular weight polypeptides from plant hydrolysate. The CHO III Prototype medium contains a zinc salt and an iron chelate. The CHO III Prototype medium contains neither insulin nor transferrin.

### **5. CHO IIIA**

The CHO IIIA medium is a serum-free medium that is a variant of the CHO III medium that encourages anchorage-dependent growth. The CHO IIIA medium is not free of animal-derived ingredients. The CHO IIIA medium is believed to be essentially protein-free, but it is not chemically defined because it contains protein hydrolysate and lower molecular weight polypeptides from plant hydrolysate. The CHO IIIA medium contains a zinc salt and an iron chelate. The CHO IIIA medium contains neither insulin nor transferrin.

### **6. CD CHO**

The CD CHO medium is a serum-free medium that can be used to culture cells in suspension. The CD CHO medium is chemically defined, protein-free and is free of animal-derived ingredients. The CD CHO medium contains a zinc salt and an iron chelate. The CD CHO medium contains neither insulin nor transferrin.

### **III. Offers for Sale**

The CHO-S-SFM and CHO-S-SFM II media were on sale in the U.S. more than one year prior to the August 30, 1996 filing date of priority application no. 60/022,881.

The CHO III prototype medium was on sale in the U.S. less than one year prior to the August 30, 1996 filing date of priority application no. 60/022,881, and more than one year prior to the August 22, 1997 filing date of priority application no. 60/056,829.

The CD CHO medium was on sale in the U.S. after the August 30, 1996 filing date of priority application no. 60/022,881, less than one year prior to the September 2, 1997 filing date of priority application no. PCT/US97/15296, and more than one year prior to the February 23, 1998 filing date of the present application.

#### ***IV. Experimental Testing Of The Media Of The Present Application***

##### ***A. Experimental Testing Of The Suspension Culture Medium***

Dr. David Epstein and Dr. Dale Gruber are co-inventors of the suspension culture medium. Dr. Epstein and Dr. Gruber are employees at Life Technologies, Inc., the assignee of the present application. Less than one year prior to the August 30, 1996 filing date of U.S. provisional application no. 60/022,881, and more than one year prior to the August 22, 1997 filing date of U.S. provisional application no. 60/056,829, Dr. Epstein and Dr. Gruber provided a sample of a serum-free medium that contained dextran sulfate to an outside researcher not employed by Life Technologies, Inc. Dr. Epstein and Dr. Gruber provided the sample to the outside researcher for the experimental purpose of determining the yield of adenovirus 5 in 293 cells cultured in the serum-free medium.

Less than one year prior to the August 30, 1996 filing date of U.S. provisional application no. 60/022,881, and more than one year prior to the August 22, 1997 filing date of U.S. provisional application no. 60/056,829, the outside researcher wrote to Dr. David Epstein and Dr. Gruber to clarify the experimental protocol and to suggest changes to the protocol. A copy of the outside researcher's letter is provided herewith, with the date, name of the researcher, and the institution masked, and is listed as document AR22 on the Form PTO-1449 filed herewith.



Dr. Epstein and Dr. Gruber wrote to the outside researcher and provided the outside researcher with further instructions for experiments. A copy of the letter from Dr. Epstein and Dr. Gruber to the outside researcher is provided herewith, with the date, name of the researcher, and the institution masked, and is listed as document AS22 on the Form PTO-1449 filed herewith.

The outside researcher prepared a report of his experimental results and forwarded his report to Dr. Epstein and Dr. Gruber. A copy of the report is provided herewith, with the medium name and lot number masked, and is listed as document AT22 on the Form PTO-1449 filed herewith.

The medium provided to the outside researcher was not free of animal-derived ingredients, was not protein-free, and was not chemically defined. The medium provided to the outside researcher contained a zinc salt, transferrin and insulin, and did not contain an iron chelate.

The medium formulation was not disclosed to the outside researcher. The medium was neither sold nor offered for sale. The outside researcher accepted three spinner flasks from Life Technologies, Inc. as payment for having performed the experimental testing of the suspension culture medium.

***B. Experimental Testing Of The Replacement Medium***

Dr. Stephen Gorfien is a co-inventor of the replacement culture medium. Dr. Gorfien is an employee at Life Technologies, Inc., the assignee of the present application. As described below, Dr. Gorfien provided media samples to outside researchers not employed by Life Technologies, Inc. for experimental purposes. Media formulations were not disclosed to the researchers. The media were neither sold nor offered for sale. Dr. Gorfien instructed the researchers to report the results of their experiments to him.

**1. *More Than One Year Prior To The Filing Of Priority Application No. 60/022,881***

More than one year prior to the August 30, 1996 filing date of application no. 60/022,881, prior to the offer of sale of the CHO III medium, and prior to the offer of sale of the CD CHO medium, samples were provided to researchers as follows.

**a. *CHO III Prototype***

7 researchers were provided with the CHO III prototype medium to determine whether the medium would support the growth of cells in suspension culture.

**b. *CHO IIIA***

5 researchers were provided with the CHO IIIA medium to determine whether the medium would support the growth of cells in adherent culture.

**2. *More Than One Year Prior To The Filing Of Priority Application Nos. 60/056,829 and 08/920,875***

More than one year prior to the August 22, 1997 filing date of application no. 60/056,829, more than one year prior to the August 29, 1997 filing date of application no. 08/920,875, and less than one year prior to the August 30, 1996 filing date of application no. 60/022,881, samples were provided to researchers as follows.

**a. *CHO III Prototype***

Prior to the offer of sale of the CHO III prototype medium, and prior to the offer of sale of the CD CHO medium, the CHO III prototype medium was provided to 3 researchers to determine whether the medium would support the growth of cells in suspension culture.

After the offer of sale of the CHO III prototype medium, and prior to the offer of sale of the CD CHO medium, the CHO III prototype medium and dextran sulfate were provided to one researcher to determine whether the dextran sulfate would inhibit cell clumping in suspension culture.

***b. CD CHO***

After the offer of sale of the CHO III prototype medium, and prior to the offer of sale of the CD CHO medium, the CD CHO medium was provided to 19 researchers to determine whether the medium would support the growth of cells in suspension culture. Three of the 19 researchers were also provided with dextran sulfate, to determine whether the dextran sulfate would inhibit cell clumping in suspension culture. One of the researchers who received dextran sulfate was also provided with an iron carrier to determine whether it could replace human transferrin.

One of the researchers, who was not provided with dextran sulfate, was provided with a lipid cholesterol mixture to use with the CD CHO medium, to determine whether the medium would support the growth of NSO myeloma cells.

***c. CHO-A-SFM Medium***

After the offer of sale of the CHO III prototype medium and prior to the offer of sale of the CD CHO medium, the CHO-A-SFM medium was provided to 2 researchers to determine whether the medium would support the growth of cells in adherent culture. One of the researchers was also provided with AlbuMAX I, which is a bovine albumin supplement.

***d. CHO IIIA Medium***

After the offer of sale of the CHO III prototype medium and prior to the offer of sale of the CD CHO medium, the CHO IIIA medium was provided to 3 researchers to determine whether the medium would support the growth of cells in adherent culture.

***3. More Than One Year Prior To The Filing Of Application No. 09/028,514***

More than one year prior to the February 28, 1998 filing date of the present application, and less than one year prior to the filing of priority application nos. 60/056,829 and 08/920,875, samples were provided to researchers as follows.

***a. CD CHO***

After the offer of sale of the CHO III prototype medium, and prior to the offer of sale of the CD CHO medium, the CD CHO medium was provided to 8 researchers to determine whether the medium would support the growth of cells in suspension culture.

***b. CHO-A-SFM***

After the offer of sale of the CHO III prototype medium, and prior to the offer of sale of the CD CHO medium, the CHO-A-SFM medium was provided to 2 researchers to determine whether the medium would support the growth of cells in adherent culture. One of the

researchers was also provided with a human albumin supplement. The other researcher was provided with AlbuMax I, which is a bovine albumin supplement.

***V. Respective Dates of Invention***

Dr. Don McClure is a co-inventor of claims 1-83 and 139-142 (the suspension medium), and is an employee at Eli Lilly and Company.

Dr. Gorfien is a co-inventor of claims 84-138 and 143-145 (the replacement medium), and is an employee at Life Technologies, Inc.

The inventions of claims 1-83 and 139-142 (McClure *et al.*) and 84-138 and 143-145 (Gorfien *et al.*) were not commonly owned at the time the McClure *et al.* and the Gorfien *et al.* inventions were made. Based on information available to the undersigned at the present time, the respective dates of invention of the McClure *et al.* and Gorfien *et al.* inventions cannot be determined at the present time.

***VI. Additional Information***

In March, 1996, Dr. Gorfien attended a talk by Dr. Michael Shuler, a researcher at Cornell University. In his talk, Dr. Shuler discussed the use of dextran sulfate to culture insect cells. Prior to the talk by Dr. Shuler, Dr. Gorfien and Dr. Epstein had discussed Dr. Epstein's use of dextran sulfate in the suspension culture medium. After the talk by Dr. Shuler, Dr. Gorfien had the idea to use dextran sulfate in the CHO III and CD CHO media.

In a poster presented at the European Society for Animal Cell Technology in May, 1996, Shiloach *et al.* reported on the development of a serum-free medium which uses a DMEM basal medium which is supplemented with  $\beta$ -mercaptoethanol, tri-iodothyronine, ExCyte, and phosphate buffer. That medium may have been commercialized by Kemp Biotech.

Dr. Bernard Massie is a researcher at The Institut de Recherche en Biotechnologie, Canadian National Research Council, in Montreal. Prior to the August 22, 1997 filing date of priority application no. 60/056,829, Dr. Massie explained to Dr. Epstein that he had modified a hybridoma serum-free medium (manufactured by Life Technologies, Inc.) for the high density culture of 293 cells. Dr. Massie did not communicate how he had modified the hybridoma serum-free medium, and Dr. Epstein does not know how Dr. Massie modified the medium.

***VII. Additional Comments***

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

An office action on the merits has not been mailed by the Examiner. Accordingly, it is believed that no fee payment is necessary.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Date: September 24, 1995

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